Early Programming Effects of Nutrition – Life-Long Consequences?

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This publication was supported by an unrestricted educational grant by the Nestlé Nutrition Institute. The institute is a not-for-profit association which was created to provide medical and scientific information to health professionals in the field of pediatric, adult and sports nutrition with latest information on nutrition and nutrition-related disorders (available at www.nestlenutrition-institute.org).
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Disclosure Statement Guest Editor
Frank M. Ruemmele is member of the Editorial committee of Annales Nestlé, which is supported by the Nestlé Nutrition Institute.
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The above articles were originally published as a supplement issue of
Annals of Nutrition and Metabolism and are reprinted here with permission
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The concept that early life events might have late-onset and life-long consequences grew over the last years in various fields and is now well established. These so-called 'imprinting events' can occur during intraterine development of the fetus/embryo, as well as during early postnatal development. The term commonly used for an effect with long-term and potentially life-long consequences is programming, such as nutritional or metabolic programming. In fact, nutritional status and nutritional interventions seem to have a major impact on the developing body – at short term, as easily understandable, but also on a long term, as supported by the concept of early programming. Epidemiological data clearly demonstrated that restricted intraterine growth due to maternal food restriction is an important contributor to coronary artery disease and future cardiovascular complications. Important data come from the Dutch Famine Birth Cohort Study analyzing pregnant women and their newborns that were exposed to a 5-month period with extreme food shortage during winter 1944/45 in the Netherlands under Nazi occupation. The cohort made a clear link between under-nourishment of the mothers during the first trimester of pregnancy and the onset of cardiovascular diseases of the newborn four decades later [1]. Thus the nutritional status of the mother during early intraterine development directly impacts on regulatory mechanisms of the embryo, causing the onset of arterial hypertension and cardiovascular disease. These observations raise several particularly important issues: what is the molecular basis of these early programming effects and is there a possibility to prevent the occurrence of future diseases, such as cardiovascular or metabolic diseases including obesity – major health concerns of the 21st century?

Research over the last ten years allowed gaining deep insight into the molecular mechanisms of nutritional programming. Epigenetic modification of the DNA in form of methylation of CpG motifs or via methylation, acetylation or eventually biotinylation of histones [2–4] is one of the main regulatory mechanisms of gene expression, particularly during development. The genomic DNA is wrapped around nuclear proteins (histones) in a very dense manner. Tightly packed DNA is largely inaccessible to transcription; however, after histone modification (methylation or acetylation) these molecules change their tertiary structure. They uncoil or unfold, thereby giving access of transcription factors to previously hidden promoter regions inducing gene expression. Most often histone modification goes along with DNA methylation which occurs at cytosine bases (CpG islands), a mechanism indispensable for genomic stability [5]. In the human genome between 60 and close to 90% of CpG islands are methylated, a potent mechanisms to reduce gene expression (gene silencing).

To analyze the potential impact of early programming via epigenetic modification of gene expression, Drs. Hanson, Low and Gluckman [6] performed an epidemiological analysis of non-communicable diseases (NCD), such as cardiovascular disease or type 2 diabetes. They highlight that cardio-metabolic diseases are endemic in the developed as well as developing world and account for more than 60% of deaths of humanity. Current strategies to prevent disease development target adults which are already affected or at high risk. Drs. Hanson, Low and Gluckman clearly indicate that these disorders might probably be preventable; however, an improved understanding of the development of disease onset is mandatory to achieve this goal. There is increasing epidemiological as well experimental and clinical evidence indicating that early life conditions may impact on later health status. The authors indicate that during development a window of epigenetic lability might exist imprinting on later life phenotype and risk to develop cardio-metabolic diseases. Major environmental factors are maternal diet during pregnancy and breast feeding as well as early postnatal feeding practice, which via epigenetic modifications will modify metabolic programs and functions. Thus prevention strategies of cardio-metabolic disease should take account of this window of opportunity in early life. This concept is largely supported by the experimental work presented and discussed by Drs. Patel and Srinivasan [7]. They demonstrate in animal models to what extent altered nutritional exposure during the postnatal period impacts on adult phenotype and health. For instance, temporary over-nourishment during the suckling period induces modifications of the hypothalamic energy circuitry predisposing to later-onset obesity. Not only an increased caloric intake, but also qualitative modifications of the composition of the diet (i.e. high carbohydrate diet without increased energy supply) leads to significant alterations of pancreatic and hypothalamic gene expression predisposing to obesity. Their work with animal models allowed
addressing the molecular basis of these effects, which are largely mediated via epigenetic modifications of genes implicated in glucose homeostasis and appetite regulation. Unexpectedly, offspring of high carbohydrate-fed female rats also demonstrated increased body weight suggesting a spontaneous transfer of the acquired phenotype to second generation, particularly with overfeeding practices during the suckling period. These experimental data from animals suggest that modifications of feeding practices during the first months of life in healthy infants may indeed contribute to future disease risk.

Early ‘malprogramming’ of vital regulatory mechanisms as response to altered nutritional exposition during the early postnatal period may lay the foundation for the development of metabolic disorders, including obesity. In keeping with these hypotheses and experimental data, Dr. Tounian [8], who analyzed the programming events leading to childhood obesity, clearly states that the excessive growth gain in obese children should be considered as a programmed disease related to various genetic variants. These variants can be genetic defects, such as mutations or polymorphisms interfering with key functions in appetite regulation, or developmentally acquired modifications of gene functions, such as epigenetic modification. Dr. Tounian points out the complexity of the adipostat, which summarizes multiple control mechanisms implicated in appetite and weight control. To develop childhood obesity, a constitutional or genetic susceptibility is necessary but not sufficient, an obesogenic environment is indispensable. But on the other hand, the same environment without genetic susceptibility will not lead to obesity. Therefore, Dr. Tounian suggests that obesity prevention strategies should be targeted to at-risk individuals instead of large schedule prevention programs for the whole population.

An additional but important player in the field of early programming particularly towards obesity is introduced by the report of Dr. Bäckhed [9]: the intestinal microflora. This microbrial environment within the intestinal tract is of primordial importance, since the gut microbiota depending on nutritional factors constitutes a large metabolic potential with direct effects on the hosts’ immune system and metabolism. Using animal models, such as germ-free mice (which are housed under strict sterile conditions), Dr. Bäckhed demonstrates the impact of the microbiota on the metabolism of the host. Germfree mice are protected against diet-induced obesity. On the other hand, the gut microbiota improves energy extraction from the diet and it can directly induce genes of the enterohepatic system. In addition, the microflora is an important ‘detoxifier’ of xenobiotic compounds. Several studies report marked differences between the gut microbiota of obese and non-obese individuals, such as a reduced amount of Bacteroidetes in obese. The obese microbiome is markedly enriched in genes favouring energy extraction and carbohydrate degradation. However, these qualitative differences in gut microbiota do not separate cause or consequence. An interesting and important observation to address this point is the fact that mice receiving the gut microbiota from obese animals gained significantly more weight compared to those animals receiving the microbiota from lean animals. Molecular targets implicated in nutrient absorption and energy storage on the host side and potentially regulated by the microbiota are angioptin-like protein 4, G-coupled receptors 41 and 43 and many others. Thus there is converging evidence that the intestinal microbiome is central to the hosts’ metabolism: on the one side the composition and biological activity of the gut bacteria is largely influenced by nutrient and diets, on the other side it actively contributes to energy extraction and absorption, thus indirectly impacting on host functions. But as shown in the germ-free model, intestinal bacteria can also directly regulate gene expression in the host.

Taken together these four reports demonstrate that the development of extremely frequent diseases, such as cardiovascular or metabolic disorders, is at least in part programmed by events very early in life. There are convincing data indicating that there is a window of opportunity for programming or malprogramming via nutritional interventions and indirectly microbial modifications of the gut microbiota with life-long consequences. The intrauterine life and early postnatal period seems to be a period of epigenetic lability, in addition the intestinal colonization process takes place during the first weeks and months after birth. Over the last decades, life style and eating habits changed profoundly in developed and developing countries. It is conceivable that modification of the environment including postnatal feeding practices contribute to the onset of adult disease. Therefore, prevention strategies of metabolic disease in at-risk adult individuals might occur too late and prevention programs should target these insults of malprogramming in the first months of life. A new area of research is open.

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References